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Abstract

Background

Human expectation of psychoactive drugs significantly alters drug effects and behavioral responses. However, their neurophysiological mechanisms are not clear. This study investigates how cocaine expectation modulates human brain responses to acute cocaine administration.

Methods

Twenty-six right-handed non–treatment-seeking regular cocaine abusers participated in this study. Changes in blood oxygenation level-dependent (BOLD) signals were measured, and online behavioral ratings during cocaine expectation and acute cocaine administration were recorded.

Results

Distinct regional characteristics in BOLD responses to expected and unexpected cocaine infusions were observed in the medial orbitofrontal gyrus (Brodmann area [BA] 11), frontal pole (BA 10), and anterior cingulate gyrus regions. Active engagement in the amygdala and the lateral orbitofrontal cortex (OFC; BA 47) by unexpected but not expected cocaine infusion was discovered. Cocaine expectation did not change BOLD responses to acute cocaine administration in a set of subcortical substrates, the nucleus accumbens, ventral putamen, ventral tegmental area, and thalamus.

Conclusions

These results suggest that cocaine expectation modulates neural-sensitivity adaptation between the expected events and the actual outcomes but did not modulate the pharmacological characteristics of cocaine. In addition, the amygdala–lateral OFC circuitry plays an important role in mediating stimulus-outcome relations and contextual factors of drug abuse.

Key Words

Amygdala, cocaine, expectation, functional magnetic resonance imaging, human brain, orbitofrontal cortex

Human expectation of the effects of psychoactive agents—both therapeutic and abused—interacts significantly with the actual effects. Alcohol and marijuana have been reported to enhance subjective effects in dependent subjects after the presentation of predictive cues (1, 2). Volkow *et al.* (3) reported that the expectation of the reinforcing effects of methylphenidate (MP) generally enhances the acute

MP effect in cocaine addicts. Other studies demonstrated that expectation of drugs, as one of the conditioned responses, significantly contributed in decreasing drug effects or drug tolerance (4). However, the issue of how drug expectation affects human drug use behavior remains primarily unsolved.

Functional magnetic resonance imaging (fMRI) has been employed to investigate roles of expectation in relation to appetitive and financial rewards in humans, by measuring changes in blood oxygenation level-dependent (BOLD) signals during reward processing (5, 6, 7). Activation in the orbitofrontal cortex (OFC) and other anterior prefrontal areas has been recorded during anticipatory periods preceding pleasant (8) and aversive (9, 10) sensory stimuli. The medial OFC has been associated with reinforcement stimuli and outcomes (11), whereas the lateral OFC has been linked to behavior modification on the basis of previous reward-related experiences (11, 12, 13, 14). However, OFC BOLD responses were also modulated by uncertainty about the outcome of reward-predicting trials (15). These studies explain the functional roles of expectation of natural and financial rewards and their relationship to neural structures in a manner detectable by fMRI. However, caution should be exercised in applying these results to drug expectation, because drugs like cocaine might act on different parts of the reward system with varying levels of strength.

Previous fMRI human studies involving acute cocaine administration attempted to account for effects of drug expectation by using a double-blind design (16) or by informing the subjects of the nature of the drug administration (17, 18). To date, no studies have explicitly investigated the effect of drug expectation on human brain responses to acute cocaine. The nature and extent of the contribution of expectation to human cocaine processing remains elusive.

Here, we describe an fMRI study in which the cocaine-addicted subjects expected either the delivery of a 20-mg/70 kg cocaine dose or a control dose of saline by a predictive visual message 4 min before infusion. It is hypothesized that concomitant cocaine-induced euphoria and craving (19) are likely derived from the interacting pharmacological effects and learned responses (20, 21), and drugs of abuse purportedly invoke a strong expectation of reward, overactivating reward, and motivation circuitry while suppressing executive control.

Methods and Materials

Human Subjects and Drug Run-Up

Detailed inclusion and exclusion criteria as well as run-up procedures for the participants were described previously in the literature (17, 22). In brief, 26 right-handed non–treatment-seeking regular cocaine abusers from the greater Milwaukee area participated in this study. A consent form approved by the Institutional Review Board was obtained from each subject before any experiments were conducted. During the consent process, participants were informed that they might receive either saline or cocaine administration during the experiment. Subjects were given an overnight stay at the hospital, ascertaining the 12-hour abstinence from cocaine before the fMRI experiment.

Although 26 right-handed, non–treatment-seeking cocaine-dependent individuals were recruited, 22 subjects completed experimental procedures in the 2-day study; 4 were eliminated, owing to apparent gradient problems with the imaging apparatus. Of these 22 subjects, 9 were eliminated owing to the

presence of motion artifacts in their datasets (translational motion more than 1.5 mm of base value in any direction, rotational motion not more than 1.5° from base position when not corrected by volume registration and regression), and 13 yielded useable BOLD data for all four fMRI runs. Of these 13 subjects, 7 experienced the expected cocaine (EC) and expected saline (ES) runs on the 1st day and unexpected cocaine (UC) and unexpected saline (US) runs on the 2nd day. The other 6 experienced UC and US runs on the 1st day and EC and ES runs on the 2nd day. As a result, subjects received order-controlled treatments of cocaine or saline.

Of the 13 subjects whose data were fully analyzed, 9 were male and 12 were black (1 Hispanic). The age (40 ± 7.5 years), education level (12 ± 1.3 years), history of cocaine use (14.5 ± 5.3 years, 4.2 ± 2 times/week), and estimated expenditure on cocaine (190 ± 170 dollars/week) of the analyzed subjects did not significantly differ from the entire population of recruited individuals.

Cocaine and Saline Infusion

As illustrated in Figure 1A, each subject received two separate scanning runs, one cocaine run and one saline run on each of the 2 days. Each run lasted for 20 min. After 4 min of a baseline scan while subjects watched a cross point at the center of a blue screen, a green bar appeared across the bottom of the screen with the message “20 mg cocaine is coming” or “saline is coming.” It gradually shrank from left to right (Figure 1B). At 7 min into the 20-min scan, when the green bar vanished, a single 20-mg/70 kg dose of cocaine in 10-mL saline volume or 10 mL saline was infused intravenously over 30 sec. In expected cocaine runs, the message “20 mg cocaine is coming” was followed by a cocaine infusion of a 20-mg/70 kg dose (the EC run). The message “saline is coming” was followed by a 10-mL saline infusion (the ES run). In unexpected cocaine runs, the message “saline is coming” was followed by a cocaine infusion of a 20-mg/70 kg dose (the UC run), and the message “20 mg cocaine is coming” was followed by a 10-mL saline infusion (the US run). The four runs were performed in counterbalanced order (Figure 1A). This cocaine dosage of 20 mg/70 kg has a comparable dopamine transporter (DAT) occupancy in humans as a 42-mg/70 kg dose (23), which was used in the intravenous treatment in the previous acute cocaine fMRI study (16). In addition, the 20-mg/70 kg dose of cocaine was used to minimize the confounding systemic effects of cocaine on the cerebrovascular system (24), although the peripheral blood pressure changes do not significantly affect the BOLD signals in the human brain (25).

Figure 1. Experimental design. Schematic of the scanning sequence, including high-resolution anatomical scan and two functional magnetic resonance imaging (fMRI) runs each lasting for 20 min **(A)**. Treatments 1 and 2 were order-balanced either with cocaine infusion or saline infusion under expected or unexpected conditions. Only one cocaine infusion each day was conducted in the 2-day experiment. The physiological monitoring and the online visual analog scale (VAS) ratings were recorded during the fMRI runs. The total imaging time lasted for about 1.5 hours. **Figure B** is a representative of a visual stimulus during cocaine expectation.

Physiological monitoring and behavioral measurements were performed, as described previously (17). The heart rate and blood pressure did not significantly change after infusion during the saline runs. Among the 13 subjects who provided useable fMRI data collection, 11 successfully furnished online behavioral data during the fMRI experiments (2 subjects had difficulty operating the joystick while in the scanner). For behavioral data analysis, mean pre-infusion visual analog scale (VAS) scores were compared with mean post-infusion scores for each of the rating types ("high," "craving," "pleasant," "nervous," and "sour") by two-sample *t* tests.

fMRI Data Acquisition

All experiments were performed on a GE Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, Wisconsin) with the multiecho segmented echo-planar imaging (EPI) with z-shimmed background gradient compensation (MESBAC) pulse sequence (26). The detailed data acquisition procedures and imaging parameters for implementing the MESBAC pulse sequence (17) to obtain reliable BOLD-weighted fMRI signals in the regions of the OFC, amygdala, and nucleus accumbens (NAc) were provided previously. In this study, each run lasted for 20 min, during which four axial slices of the inferior brain (relative to the anterior commissure) were imaged every 8 sec with the MESBAC pulse sequence (240-mm field-of-view, flip angle = 50°, echo time = 30 msec, 150 reps, 128 × 64 matrix with 5-mm slice thickness). The four MESBAC slices were interleaved with single-shot EPI acquisitions of 16 slices encompassing the rest of the brain with the same imagine parameters as the MESBAC sequence except the 64 × 64 matrix. Dummy echoes were obtained within each repetition-time interval to obtain steady-state longitudinal magnetization. After the functional imaging runs, high-resolution (.94 mm × .94 mm in-plane, 1-mm slice thickness) T_1-weighted whole-brain anatomical images were obtained with a spoiled gradient recalled acquisition in the steady state (GRASS) pulse sequence (27).

fMRI Data Analysis

Statistical analysis of the 13 fMRI datasets was performed with Analysis of Functional Neuroimages (AFNI) software, as described previously (17, 28). The BOLD responses of the cocaine and saline runs were fitted with a nonlinear least-squares simplex algorithm to a difference-of-exponents model based on the single-dose single-compartment pharmacokinetics of cocaine (29). The area between the fitted curve and the baseline for each voxel was calculated by numerical integration and normalized, using the area between the baseline signal and zero. The resulting quotient was expressed as a percentage (AUC%), associated with each brain voxel. The voxelwise AUC% maps were transformed into a common Talairach space for analysis with a 2 × 2 repeated-measures voxelwise analysis of variance (ANOVA) to determine main effects of expectation (cocaine or saline, as displayed above the shrinking bar) and cocaine infusion (cocaine or saline infusion), in which the individual subjects were a random factor. The *F* statistic parameters were acquired to find the presence of each main effect. A cluster threshold at the $p < .05$ level was used (30), accounting for the multiple comparisons problem (individual voxel threshold at $p < .03$, minimum cluster size = 1024 μL). Once the main effects of expected and administered treatments were established, paired *t* tests of post-infusion AUC% were used to confirm activation by expected- (EC vs. ES, Figure 2A, Table 1) and unexpected-cocaine infusion (UC vs. US, Figure 2B, Table 2) and the difference in AUC% between UC and EC conditions (Figure 2C, Table 3). The centroid coordinates listed in the Results (Table 1, Table 2, Table 3) are calculated by the AFNI program

3dclust as the center-of-mass of the corresponding cluster. In the case of clusters encompassing multiple regions, the locations of local maximum *t* scores were reported as the centroids.

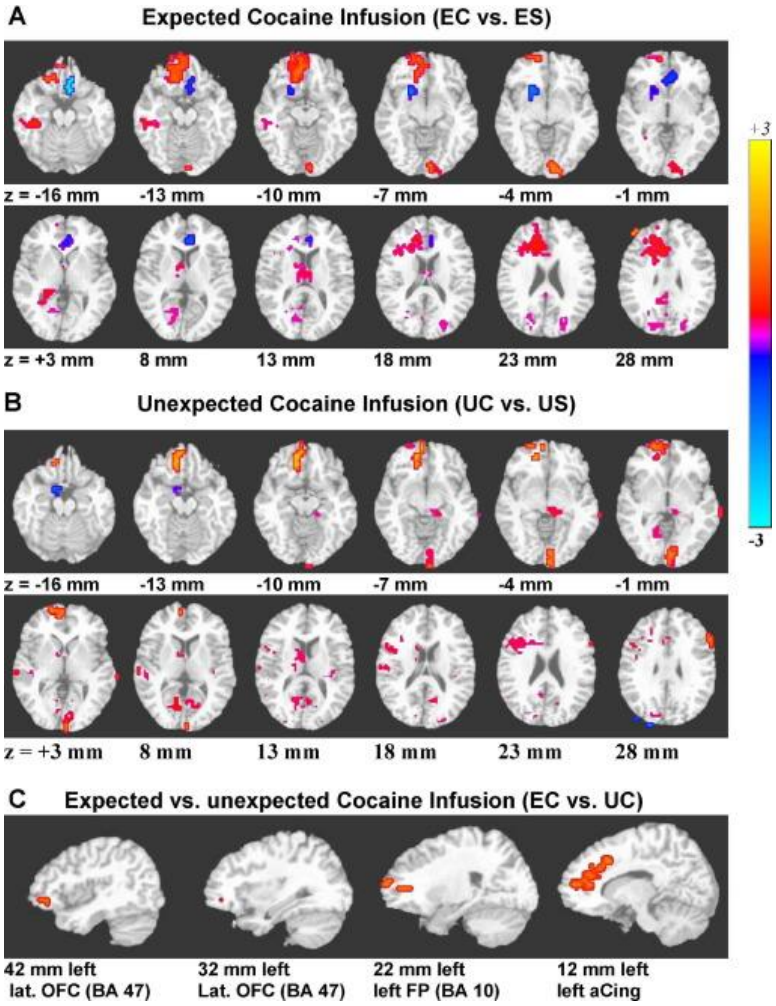

Figure 2. Activation maps. Activation maps of expected-cocaine infusion (EC vs. ES; **Figure A**), unexpected-cocaine infusion (UC vs. US; **Figure B**), and differential activation of expected- versus unexpected-cocaine infusion (EC vs. UC; **Figure C**), respectively. The maps were generated by voxelwise paired *t* tests of area-under-the-curve percentage (AUC%) of the acute cocaine post-infusion from 13 subjects (the color bar on the right represents the *t* values). Significance threshold is set to $p < .05$, after application of cluster algorithm. Left is left for the axial slices.

Table 1. Activated Human Brain Regions ($p < .05$ after clustering) After Expected Cocaine Infusion (EC vs. ES)

Anatomical Region	**Side**	**Talairach (mm)**			**Brodmann Area**	**BOLD Polarity**	**Cluster Volume (µL)**
		X	**Y**	**Z**			
Nucleus Accumbens	L	−14	10	−5		–	960
Ventral Putamen	L	−21	18	−7		–	[a]
OFC: MOG	L	−10	47	−12	11, 13, 11[b], 14[b]	+	4596

OFC: Frontal Pole	L	−11	55	−5	10, 10[b]	+	832
OFC: Caudal OFC/SCC	R	9	33	−21	11, 13[b], 25[b]	−	1664
Anterior Cingulate	L	−14	22	30	24, 32	+	17024
DLPFC	L	−38	25	32	9	+	[a]
Anterior Insula	L	−33	16	14	13	+	[a]
Anterior Cingulate	R	3	32	5	24	−	1856
Caudate	L	−6	1	7		+	2112
Thalamus: Medial Dorsal	L	−6	−14	12		+	[a]
Thalamus: Medial Dorsal	R	5	−14	12		+	[a]
Middle Frontal Gyrus	L	−30	9	47	6	+	1024
Postcentral Gyrus	L	−23	−34	63	3	+	1024
Postcentral Gyrus	R	23	−35	63	3	+	960
Precentral Gyrus	L	−10	−20	64	6	−	1216
Precuneus	L	−18	−75	35	7	+	1216
Cingulate Gyrus	L	−9	−43	31	31	+	[a]
Precuneus	R	22	−57	46	7	+	1472
Inferior Parietal Lobule	R	39	−34	42	40	+	1344
Cuneus	L	−16	−70	17	18, 30	+	4992
Cuneus	R	20	−79	25	18, 19	+	3904
Fusiform Gyrus	L	−41	−30	−15	20	+	1344
Middle Temporal Gyrus	L	−54	−29	−14	20	+	[a]
Parahippocampal Gyrus	L	−24	−40	4	30	+	896
Lingual Gyrus	R	7	−89	−7	18	+	1152
Cerebellum: Culmen	R	31	−43	−24		+	1664

EC, expected cocaine; ES, expected saline; BOLD, blood oxygenation level-dependent; OFC, orbitofrontal cortex; MOG, medial orbital gyrus; SCC, subcallosal cortex; DLPFC, dorsal lateral prefrontal cortex.

[a]An activation site that belongs to the cluster listed in the row directly above.

[b]Alternative designations for orbitofrontal cortex (OFC) regions (68).

Table 2. Activated Human Brain Regions ($p < .05$ after clustering) After Unexpected Cocaine Infusion (UC vs. US)

Anatomical Region	**Side**	**Talairach Origin (mm)**			**Brodmann Area**	**BOLD Polarity**	**Cluster Volume (µL)**
		X	**Y**	**Z**			
OFC: MOG	L	−10	44	−10	11, 10, 11[a]	+	2176
OFC: Frontal Pole	L	−12	60	−1	10, 10[a]	+	1664
Amygdala	L	−13	−1	−16		−	1088

Parahippocampal Gyrus	L	−14	2	−18	34	–	[b]
Parahippocampal Gyrus	R	14	−29	−5	35	+	768
Anterior Cingulate	L	−5	−11	42	24	+	896
Caudate	L	−8	0	11		+	2176
Thalamus	L	−12	−11	14		+	[b]
Medial Frontal Gyrus	L	−22	29	28		+	768
DLPFC	L	−36	15	25	9, 46	+	7552
Anterior Insula	L	−40	3	14	13	+	[b]
DLPFC	R	55	20	28	9	+	1280
Posterior Insula	R	35	−27	13	41	+	1152
Posterior Cingulate	L	−7	−51	22	31	+	832
Precuneus	L	−17	−53	38	7	+	3840
Cingulate Cortex	L	−6	−41	31	31	+	[b]
Inferior Parietal Lobule	R	39	−30	43	40	+	1664
Cuneus	L	−23	−80	22	18	+	1856
Cuneus	L	−12	−63	7	30	+	2624
Cuneus	R	21	−88	18	18	+	832
Cuneus	R	8	−63	12	18	+	1664
Posterior Cingulate	R	2	−60	11	30	+	[b]
Middle Occipital Gyrus	R	33	−74	16	19	+	768
Transverse Temporal Gyrus	L	−62	−16	10	42	+	1088
Superior Temporal Gyrus	L	−35	−47	22	22	+	1152
Superior Temporal Gyrus	L	−49	−26	6	41	+	896
Superior Temporal Gyrus	L	−53	−53	12	39	+	768
Lingual Gyrus	R	3	−87	0	18	+	1856
Cerebellum: Culmen	R	37	−41	−26		+	2560

UC, unexpected cocaine; US, unexpected saline; other abbreviations as in Table 1.

[a]Alternative designations for OFC regions (68).

[b]An activation site that belongs to the cluster listed in the row directly above.

Table 3. Sites of Cocaine Activation Related to Expectation

Anatomical Region	**Side**	**Talairach (mm)**			**Brodmann Area**	**Cluster Volume (µL)**
		R/L	**A/P**	**S/I**		
OFC: Lateral Orbital Gyrus	L	−43	37	−6	47, 47/12[a]	1024

OFC: Frontal Pole	L	−18	56	5	10, 10[a]	1152
Anterior Cingulate	L	−15	44	16	24, 10	3520
Parahippocampal Gyrus	R	38	−14	−19	34	960

These activated human brain regions ($p < .05$ after clustering) were obtained by comparing the expected cocaine run with the unexpected cocaine run (EC vs. UC).

Abbreviations as in Table 1, Table 2.

[a]Alternative designations for OFC regions (68).

To evaluate different temporal characteristics present in expected- and unexpected-cocaine reward-conditions, clusters of spatially contiguous and significantly activated voxels were selected as regions-of-interest (ROIs). These ROIs, on the basis of the cluster analysis of paired *t* tests, form the anatomical loci of the activated OFC regions (Figures 3A–3D) and the mesolimbic regions (Figures 4A–4F). Before averaging across subjects, the selected BOLD time courses were normalized as percentages of baseline magnitude.

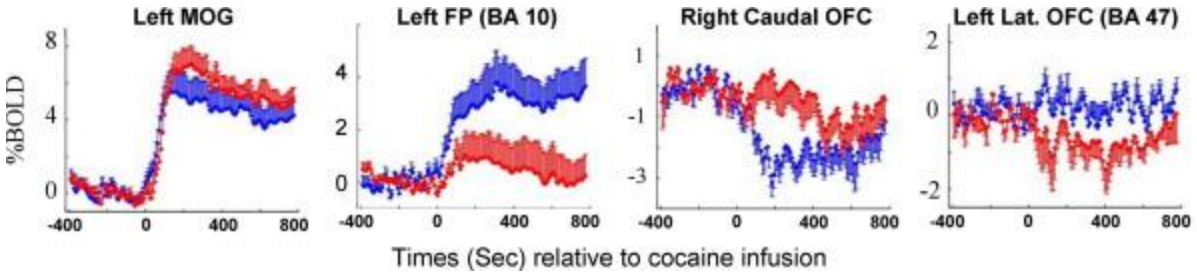

Figure 3. Differences in blood oxygenation level-dependent (BOLD) responses in the orbitofrontal cortex (OFC) regions under expected (blue) and unexpected (red) cocaine infusions. Time series of four regional average plots (**Figures A–D** for the left medial orbital gyrus [MOG], left frontal pole [FP], right caudal OFC [cOFC], and left lateral OFC, respectively) obtained across subjects ($n = 13$). Error bars denote 1 SD. Horizontal axis is time relative to cocaine infusion (sec), and vertical axis is %BOLD magnitude relative to pre-infusion baseline.

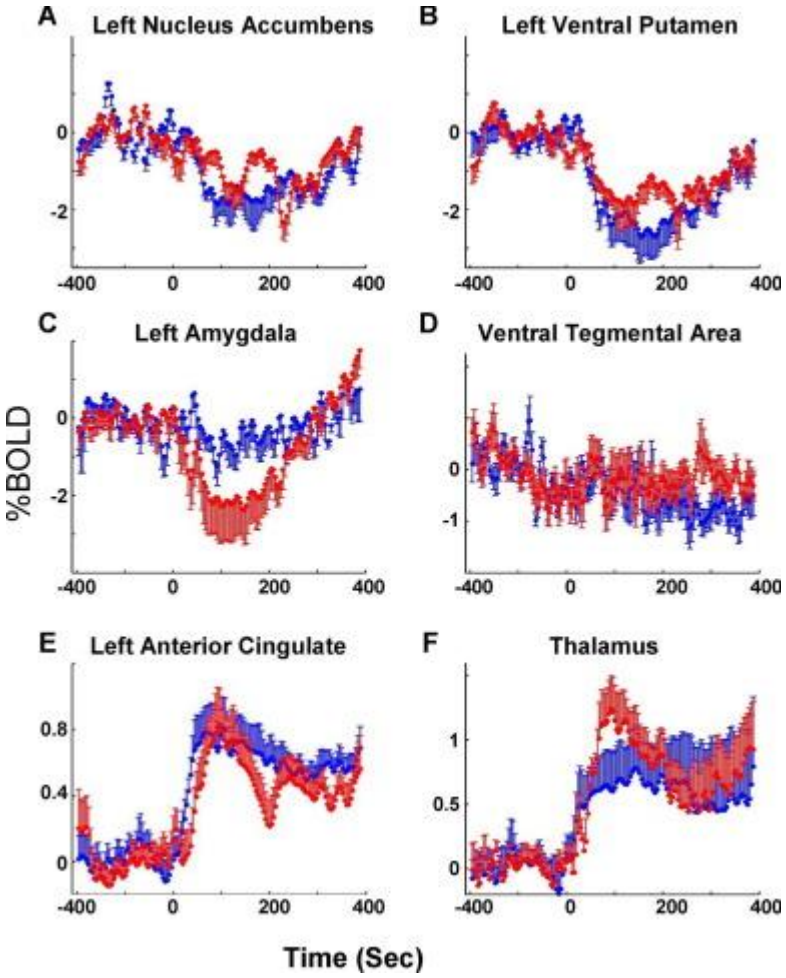

Figure 4. Differences in blood oxygenation level-dependent (BOLD) responses in the paralimbic and subcortical regions under expected (blue) and unexpected (red) cocaine infusions. Error bars represent 1 SD. The horizontal axis represents time, in sec, relative to the start of cocaine infusion. The vertical axis represents changes in BOLD magnitude, as a percentage of the pre-infusion baseline magnitude. **A:** left nucleus accumbens. **B:** left ventral putamen. **C:** left amygdala. **D:** ventral tegmental area. **E:** left anterior cingulated. **F:** thalamus.

Results

Behavioral Measures

Throughout each fMRI run, the subject reported his or her subjective feelings of five variables by moving a joystick-controlled cursor below VAS ratings of high, craving, pleasant, nervous, and sour (Figure 1B). After cocaine infusion, there were several behavioral VAS ratings that significantly changed. For example, the mean of the high VAS ratings was significantly elevated from pre-infusion baseline levels in both the unexpected-cocaine (UC) (two-sample unpaired *t* test, $p < .005$) and expected-cocaine (EC) runs ($p < .001$). The mean of the post-infusion craving ratings was elevated from pre-infusion baseline levels in both the UC ($p < .03$) and EC runs ($p < .05$). The mean of post-infusion pleasant VAS ratings was significantly elevated from pre-infusion levels in the EC run ($p < .02$) but not in the UC run. However, the means of post-infusion high, craving, and pleasant ratings were not

significantly different between the UC and EC runs. No significant differences in nervous or sour VAS ratings were discovered among the UC, EC, expected saline (ES), and unexpected saline (US) runs.

Brain Regions Activated by Expected- and Unexpected-Cocaine Infusion

The results from the 2 × 2 ANOVA showed that the effects of expectation were occurring in several regions, including the left and right dorsal lateral prefrontal cortex (dlPFC), the left dorsal cingulate, the left and right lateral OFC, the right medial OFC, and the left lingual gyrus (*F* test, $p < .05$ after clustering). The main effects of the infusion were significant in the NAc, amygdala, medial and lateral OFC, frontal pole (FP), subcollosal cortex, thalamus, medial frontal gyrus, precuneus (PCu), and culmen of the cerebellum (*F* test, $p < .05$ after clustering). Additionally, significant expectation × infusion interaction effects were present in voxels (*F* test, $p < .05$) residing within the left ventral putamen (VPut), the left and right lateral OFC, the left and right amygdala, the left anterior cingulate, the right superior temporal gyrus, and the left parahippocampal gyrus (PHG). However, the interaction effects were not present in enough contiguous voxels to form significant clusters.

On the basis of the results of the ANOVAs' indication that the two factors significantly altered neural activities, further evaluations of paired *t* tests among experimental conditions were conducted by the clustering of voxelwise statistics in AFNI software (28). Six paired tests were conducted: ES versus UC, UC versus EC, EC versus US, US versus ES, ES versus EC, and US versus UC. Because there were very few clusters of significantly activated voxels found in the ES versus US pair (only in the right lateral OFC and the left cerebellum), the ES and US results were considered in subsequent analysis to represent the same baseline condition. Therefore, only three pairs of EC versus ES, UC versus US, and EC versus UC are presented in detail, with cocaine infusion described as the reward outcome.

In the test evaluating expected-reward outcome (EC vs. ES), significant AUC% (positive and negative) relative to baseline was found in several brain regions (Figure 2A, Table 1). Positive AUC% effects were found in several cortical areas, including the left medial orbital gyrus (MOG), FP, anterior insula, anterior cingulate gyrus (ACing), PHG, dlPFC, caudate, middle temporal gyrus, bilateral thalamus, postcentral gyrus, PCu, cuneus, right lingual gyrus, and culmen of the cerebellum. Negative AUC% clusters were found in several paralimbic areas, including the NAc, VPut, right ACing, and caudal OFC (cOFC).

In the test of unexpected-reward outcome (UC vs. US), the positive AUC% effects (relative to US AUC%) were found in the left MOG, FP, ACing, caudate, anterior insula, transverse temporal gyrus, cingulate cortex, bilateral DLPFC, cuneus, posterior cingulate cortex, right PHG, posterior insula, lingual gyrus, and culmen of the cerebellum. The negative signals were found in the left amygdala and PHG (Figure 2B, Table 2).

In the test of expected- against unexpected-reward outcome (EC vs. UC), clusters depicting significantly greater AUC% for the EC condition appeared in the left lateral OFC (BA 47), FP (BA 10), ACing (BA 24), and right PHG (Figure 2C, Table 3).

The different temporal characteristics, under expected- and unexpected-cocaine reward-conditions, were shown in Figure 3, Figure 4. The distinct differences in BOLD responses to expected- and unexpected-cocaine infusion occurred in the region of FP (Figure 3B). In addition, the active engagement in the lateral OFC (Figure 3D) and amygdala (Figure 4C) by unexpected (red curves) but

not expected cocaine infusion (blue curves) suggests that the amygdala–lateral OFC circuits are substrates of evaluative functions mediating stimulus-outcome relations and contextual factors of drug use. In addition, cocaine infusion activated a set of subcortical substrates, the NAc, VPut, ventral tegmental area, and thalamus, with limited sensitivity to expectation, implying that the BOLD responses in these regions were primarily determined by the pharmacological characteristics of cocaine.

Discussion

Expected- and unexpected-cocaine infusion activated a common set of neural substrates. The brain areas commonly activated by expected- and unexpected-cocaine infusion (Table 1, Table 2) are in general agreement with results of our previous study (17), with additional loci of activation due to the whole-brain coverage of the BOLD acquisition. This pattern might indicate a set of neural substrates related to the pharmacological and behavioral effects of cocaine. The ventral striatum (NAc and VPut), cingulate gyrus, thalamus, and OFC, among other regions, were significantly activated by cocaine infusion, whether or not the shrinking bar message correctly predicted it (Figure 2, Figure 4). As reported previously (17), the ventral striatum experienced a cocaine-induced negative BOLD change. The latter might reflect augmented DA release in the NAc and other mesocorticolimbic target fields, which serve as a key mechanism of drug-seeking and drug-reinforcement (31, 32). This result seems to agree with animal studies reporting reduced striatal cell excitability (33), mean firing rates (34), and glucose use (35, 36) after cocaine administration. The consistent BOLD decrease in the ventral striatum, an established site of cocaine-induced changes in dendritic spines (37), might then mainly reflect the inhibitory effect of a pharmacologically increased local DA concentration (38) rather than a sensitivity to environmental factors.

Comparison of post-cocaine infusion BOLD signals acquired in the EC and UC conditions found that expectation had significant effects on the hemodynamic responses in the OFC, ACing, right parahippocampal cortex, and left amygdala. These results are consistent with a recent positron emission tomography (PET) investigation that described expectation-enhanced regional brain metabolic effects of oral MP in cocaine abusers (3). A detailed discussion of the effects of expectation on cocaine-induced BOLD signals is provided in the following text.

The heterogeneous and context-sensitive OFC response to cocaine exhibited multiple roles in drug reward. Expected- and unexpected-cocaine infusion invoked significant BOLD responses in the left MOG (BA 11; Figure 3A), FP (BA 10; Figure 3B), right cOFC (Figure 3C), and left lateral OFC (BA 47) (Figure 3D). These results are consistent with the conclusions of recent neuroimaging studies in that the predicted reward value (6, 12, 39, 40) and subjective pleasantness of reinforcers (11) activate the OFC region. A recent review suggested that the human OFC links the reward value of stimuli with hedonic qualities (41). Dysfunction of the OFC induced by physical damage has been linked with compulsive reward-seeking behavior and insensitivity to the changing reward value of stimuli (14, 42), a condition that resembles compulsive drug use in the face of severely adverse consequences (43). Enhanced glucose use in the medial OFC has also been implicated in PET studies of both spontaneous and cue-induced cocaine craving in cocaine addicts (44, 45), suggesting a motivational role for this region (45, 46). A more recent PET study highlighted BA 11 as a primary site of MP-induced activation in cocaine addicts (47). In the present study, the left MOG locus contained the voxels with the BOLD

increases of the greatest magnitude (Figure 3A), probably reflecting reinforcement valuation in cocaine-addicted humans.

In the FP (Figure 3B), the BOLD responses were significantly associated with the post-infusion high and pleasant ratings in both EC and UC conditions. However, the magnitude of BOLD signal change after the EC infusion was substantially greater than that after the UC infusion (peak BOLD 3% vs. 1.5%). The FP is an executive region functionally distinguished from other prefrontal cortical areas by additive demands imposed by integrating simultaneous cognitive activities (48). Frontal pole activity has been shown by BOLD fMRI to be particularly sensitive to the interaction of reward expectation and decision-making (49). The augmented positive BOLD response in the area could therefore be a reflection of a cocaine reinforcement process superimposed on a cocaine expectation process, resulting in elevated mood, as reported by the differentially enhanced pleasant VAS ratings. The cocaine expectation presumed to be associated with cue-induced craving might also influence planning and decision processes, located in the prefrontal cortex (50), and have a critical role in drug procurement (46).

Although it is plausible that the subjects require additional time to register the infusion as cocaine and not saline in the UC run, an intriguing question remains: Why was the smaller BOLD signal in FP maintained in the UC run rather than in the EC run? One would assume that the same amount of cocaine (20 mg/70 kg) should produce similar BOLD responses in the post-infusion periods of the two cocaine runs, but the observed data compellingly demonstrated long-term modulation by expectation activity. One possible mechanism for this effect is the adaptation of the mesocorticolimbic system to reward-predicting stimuli (51). In the UC run, the subjects' DA neurons might have adapted to a low expected reward value (an infusion of saline), resulting in a less pronounced FP BOLD response and a slower behavioral response to the cocaine infusion. In the EC run, subjects were informed that "20 mg cocaine is coming," and the same neurons might have attained a greater sensitivity to the subsequent cocaine infusion. When the expected cocaine was administered, the higher DA-mediated "gain" might then have accommodated more robust FP BOLD changes and an accelerated behavioral response.

Emergence of an Amygdala–OFC Circuit

The amygdala seems to be engaged by cocaine administration in the UC runs but not in the EC runs (Figure 4C), analogous to the results found for the left lateral OFC (Figure 3D). The negative BOLD responses in the amygdala and the lateral OFC might represent the neural adaptation from the expected-saline infusion to the unexpected-cocaine infusion. The difference caused by expectation contingence might explain the inconsistency of results among the previous acute cocaine fMRI studies (16, 17).

The lateral OFC region (BA 47) and amygdala seemed to be activated in concert with a negative BOLD response. This result suggests an engagement of an amygdala–orbitofrontal circuit associated with reward expectancy (52) but contradicts the notion that these regions are critical to compulsive cocaine abuse (53). Connected bidirectionally with the OFC, the basolateral amygdala has been identified by recent research in stimulus–reward learning, a process that requires sensitivity to the context of reinforcing stimuli (54). The BA 47 region, also described as more sensitive to unexpected MP administration than expected MP (3), has been postulated to have a role in reward processing involving the suppression of previously established reward-related responses (55). Converging evidence from lesion experiments of the amygdala–OFC interaction in rats (56, 57) and primates (58,

59, 60) and from human patients with OFC deficits (14) suggests that this link is crucial for appropriately processing changes between predicted outcome and acquired value. Cocaine-experienced rats (61, 62) and monkeys (53) were reported to have deficits in OFC-dependent learning functions.

The context-specific negative BOLD response also implies that the cocaine-related function of the lateral OFC and amygdala is separate from the motivational circuit involving the medial OFC (BA 11). Because the cocaine-induced craving can be conceptualized as the conscious representation of a motivational state (16), a lack of BA 47 and amygdala BOLD effects in the EC condition strongly indicates this separation. This pattern also suggests that the BA 47–amygdala BOLD response is most likely associated with the context of drug reward and not the pharmacological aspects of the cocaine stimulus. The partial correspondence (significant in the UC run only) found between the lateral OFC cocaine BOLD response and high and craving ratings most likely describe an epiphenomenon and not a causal relationship. The emergence of this distinct circuit could facilitate the separation of neural substrates involving different neuropsychological and neurobiological processes of cocaine addiction, an objective also pursued in ongoing animal research (36, 61, 63).

Limitations

The fMRI BOLD method is a direct measure of the hemodynamic response to neural activity, while serving as an indirect measure of neural activity. Although the underpinnings of BOLD responses to a variety of stimuli have been fruitfully investigated (64, 65, 66), specific linkage between hemodynamic changes and underlying neural activity needs further characterization. A particular source of difficulty in pharmacological fMRI experiments is that neural chemical information, such as changes in dopamine or glutamate levels in a variety of brain regions, before or after drug administration, is difficult to estimate (67). In addition, although the fMRI BOLD method provides a better temporal resolution than positron emission tomography 18F-fluorodeoxyglucose (PET-FDG) method, the BOLD response is a relative measure to a prestimulus baseline and not a gauge of absolute changes in brain activity. Efforts have been advanced to measure absolute changes in regional cerebral blood flow with the arterial spin labeling technique. Since Talairach atlas is quite poor in terms of OFC nomenclature, further designations were done with reference to Petrides and Pandya (68).

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